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Paving a regulatory pathway for phage therapy

Europe should muster the resources to financially, technically and legally support the introduction of phage therapy

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The increasing resistance of bacteria to antibiotics is a significant threat to human health and is a direct result of the excessive and improper use of these drugs. In 2007, multidrug-resistant bacterial strains infected more than 400,000 people in Europe and 25,000 patients died from the infections [1]. 'Superbugs' also have considerable economic impact: extra hospital costs and related productivity losses amount to more than €1.5 billion per year in the European Union. In the USA, infections caused by multidrug resistant bacteria lead to US$20 billion in additional health-care costs and US$35 billion societal costs annually [2]. The situation is about to get worse, as there are only a few drugs left to treat multidrug-resistant bacterial strains, and the first strains that are resistant to even these last-resort antibiotics have already emerged. Moreover, there is a dearth of genuinely novel antibiotics in the development pipeline.

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Various proposals have been made to address the problem. These range from the more-prudent use of existing antibiotics or better hygiene, to providing incentives to the pharmaceutical industry to develop novel drugs. In addition, the use of bacteriophages, or phage therapies, to kill specific pathogens without harming the majority of harmless, commensal bacteria has received increasing attention during the past decade, but little has been done to capitalize on this interest and implement phage therapies in the clinic.

The application of bacteriophages to treat infection dates back to around the 1920s. Today, phage therapies are routinely used in countries such as Georgia and Poland, but countries in western Europe abandoned such therapy after the introduction of antibiotics. Only a handful of clinical trials are ongoing and some are taking place in countries where European regulatory standards do not apply. Elsewhere, phage therapies are only applied sporadically in specialized medical centres for the *ad hoc* treatment of patients with severe infections. At this time, the greatest hurdle to the medical use of bacteriophages in Europe is the lack of an appropriate regulatory framework that appreciates the concept and specifics of this approach to support its application in the clinic. Part of the problem is that whether phage therapies are medicinal products or something completely different is unclear under current European legislation. Implementation and regulation of their use is therefore challenging.

The current legal framework for the use of medicines in Europe is mainly dictated by European directive 2001/83/EG, which outlines the European Community code relating to medicinal products for human use. This directive was passed into law more than 10 years ago. It defines any substance or combination of substances used to treat or prevent disease

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in humans as human medicinal products and, therefore, makes them subject to specific requirements relating to safety, quality and efficacy. How phage therapies should be defined remains in question.

Bacteriophages are viruses that specifically attack bacteria and can be used to control, treat or prevent infectious diseases (Sidebar A). By controlling bacterial overgrowth, bacteriophages can re-equilibrate the host–bacteria balance and consequently they can indirectly restore physiological functions and boost the immune system. According to the definitions in the directive and the national legislation based on it, bacteriophages could be considered to be human medicinal products. The consequences of classifying them in this way would be far-reaching: phage therapies would require assessment in large clinical studies to demonstrate safety and efficacy. A strength of phage therapies is that they can be tailored to each patient and to each patient's bacterial infection. This flexibility is not fully compatible with the approach of the directive. In fact, bacteriophages are not mentioned in the current legislation, and the technical assistance or documentation that could be used to prepare a regulatory dossier does not exist.

Nevertheless, if we are to introduce phage therapy into clinical practice, they must be regulated according to the directive. To address its limitations, therefore, and in order to draft (Sidebar A) appropriate regulatory protocols for use, it is first necessary to define under which category of human medicinal products bacteriophages fall. The first category includes conventional small molecules or synthetic human medicinal drugs, such as aspirin, that can be described and researched in a standardized manner. From a functional point of view, such products are not comparable to bacteriophages because they operate in entirely different ways. Bacteriophages kill their specific bacterial host cells through bacterial lysis, which causes the release of new bacteriophage virions. When the targeted bacterial density drops below the detection threshold, the bacteriophages are removed by the reticulo-endothelial system and the therapeutic intervention becomes self-terminating. Also unlike standard drugs, bacteriophages mutate and co-evolve with their host bacteria, an evolutionary 'arms race'.

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The second category of biological human medicinal products, which includes vaccines, seems more suitable, but it does not encapsulate all the features of phage therapies. From a general structural point of view, a bacteriophage is a protein-encapsulated nucleic acid genome. Moreover, they might be collected from a biological source, for example released from bacteria or collected from a patient's tissues or fluids (for instance from wounds) or from wastewaters. Like vaccines, bacteriophage-based products used in humans need to be updated over time—especially when bacteria develop resistance—just as the flu-vaccine cocktail is tailored anew each year. Bacteriophages, however, do not produce active immunity against a specific pathogen as 'regular' vaccines do. Rather, they are antimicrobials, with a secondary competence of boosting the immune system. As such, they are perhaps better considered as similar to therapeutic vaccines.

Therapeutic vaccines fall under a third category of human medicinal products, the advanced-therapy medicinal products (ATMPs). ATMPs are defined in directive 2001/83/EC as complex therapeutic products for gene therapy, cell therapy or tissue regeneration, and have their own regulatory framework. Obviously, though, natural bacteriophages are not somatic cells or tissue-engineered medicinal products and are not natural products used in gene therapy, since they are not genetically modified.

The conclusion from the arguments presented above is that phage therapies should probably be classified as biological human medicinal products, despite the poor fit with this classification. Phage therapies do not fit into a single category perfectly, but this choice would be in accordance with the current UK practice of classifying bacteriophages.

If bacteriophages are regarded as human biological medicinal products, they must adhere to the relevant legal framework: any therapy has to demonstrate safety and efficacy and conform to quality standards. Bacteriophages exist ubiquitously in the environment, including in the human body. They specifically infect certain bacteria, but do not attack other bacterial strains or eukaryotic human cells. To assume that bacteriophages will be safe for therapeutic use and ought not to require extensive studies that would delay their clinical use, therefore, seems appropriate. Even so, clinicians should prospectively collect and register data and clinical outcomes of phage therapies to create a body of information for further research and on which applications can build.

In regard to efficacy and safety, only virulent, exclusively lytic phages are generally considered to be clinically useful because they kill their host cells and do not integrate into the bacterial host genome. Therefore, the presence of temperate bacteriophages must be strictly excluded. Detailed molecular characterization of the bacteriophage genome is also mandatory to exclude the presence of any toxin genes or antibiotic-resistance genes.

With respect to quality, a combination of physical, chemical and biological tests could be used to characterize bacteriophage-based products, together with standard quality control procedures applied to the production process. Bacteriophages should be produced in a non-pathogenic bacterial host and the final therapeutic preparations must be pure (absent of residual contaminating bacteriophages and other host cells), sterile, apyrogenic and pH neutral [3]. Such a focused approach to guarantee safety, quality and efficacy could enable clinicians to quickly prepare phage therapeutics against severe infections with multidrug-resistant pathogens.

The current regulatory regime for human biological medicinal products, which implies the conduct of clinical trials and the submission of a full product dossier compliant with directive 2001/83/EG, imposes expensive and time-consuming overheads on the urgent development of phage therapies. If we consider the example of a patient currently infected with a multidrug-resistant bacterial strain who needs immediate treatment because antibiotics have failed, the need to conduct clinical trials and compile dossiers is not feasible within the time frame required to develop a targeted *ad hoc* therapy, and would not allow timely treatment of the patient. Isolation of a bacteriophage to combat the infection, preparation of a therapeutic dose and its administration to the patient needs to be done within days. Under the human biological medicinal product framework, we would have to wait 8–10 years until clinical studies have demonstrated safety and efficacy.

Another problem is the massive cost of conducting clinical studies. Non-profit clinics and research institutes will not be able to shoulder the financial burden of a regulatory regime originally designed for drug development by pharmaceutical companies. Some companies, such as Eli Lilly, have invested in bacteriophage-based products or cocktails for human treatment, but the host-specificity of phage therapies excludes uniform production and clinical application. Large-scale production of natural bacteriophages might be helpful in some instances, such as in cases of epidemic outbreaks or in clinical programmes where phage cocktails are regularly updated, but the full therapeutic potential of natural bacteriophages can only really be exploited through a patient-specific approach.

The most likely places that patient-specific phage therapies would be administered are hospitals, in close collaboration with associated microbiological laboratories that would select and isolate the most suitable bacteriophages. This approach would require a simplified regulatory framework, given that neither time nor money is available. From this perspective, bacteriophage therapy resembles the historical context of ATMPs, which were mainly developed at clinics and academic research institutions and were only recently brought under the human medicinal product legislation (regulation 1394/2007). The legislation exempts hospitals from the regulatory framework if a cell therapy is applied under the direct supervision and prescription of a medical doctor for a specific patient (article 28 of regulation [EC] No. 1394/2007), but for ATMPs, national rules apply instead.

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Sidebar A | Further reading

d'Herelle F (1917) *C R Acad Sci* **165:** 373–375.
In this historical paper, the first isolation of bacteriophages for use in treatment and prophylaxis of infectious diseases is described.

Kutateladze M, Adamia R (2010) *Trends Biotechnol* **28:** 591–595.
The authors report on the growing body of literature describing the validation of the use of bacteriophages for therapy and prophylaxis in the war against drug-resistant bacteria.

Pirnay JP *et al* (2011) *Pharm Res* **28:** 934–937.
The authors stress the importance of a *sur-mesure* approach for phage therapy.

Merabishvili M *et al* (2009) *PLoS ONE* **4:** 1–10.
A quality-controlled small-scale production of a well-defined bacteriophage cocktail for use in human clinical trials is described.

As argued above, bacteriophages should probably be classified as human medicinal products. Unfortunately, directive 2001/83/EG does not provide a hospital exemption for these. It does state, however, that it "shall not apply to any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magisterial formula)". Even if this clause allowed hospitals to bypass the costly requirement to demonstrate safety and efficacy, hospital pharmacists can only use licensed products as components for magisterial preparations. Since natural bacteriophages are not licensed products, this regulatory bypass would be difficult to implement.

How then can the regulatory framework be adapted to allow hospitals to design and administer tailor-made phage therapies? Although regulators are responsible for applying regulations, a regulation itself can only be changed through legislative action. We suggest an adapted regulatory framework, inspired by the existing legislation governing ATMPs, which includes exemption for the hospital-based use of cell and gene products and therapies. Hospitals should be granted exemption for biological human medicinal products, accompanied by specific regulation for phage therapies developed from natural bacteriophages with regard to safety, potency, purity and toxicity. Pharmaceutical companies developing

products based on natural bacteriophages would still have to abide by the normal regulations that apply to biological medicinal products. Thus, such a regulatory framework would distinguish between the hospital-based (tailor-made) use of natural bacteriophages in patients and the industrial production and distribution of uniform phage products. Quality and safety criteria would be specified and efficacy documentation required, but it would allow treating physicians to fully exploit the coevolutionary aspects of natural bacteriophages for the benefit of patients (Sidebar A).

It is necessary to start talking to regulators and legislators and persuade them of the prudence of a dedicated legal framework for bacteriophage therapy. Doing nothing to address the growing bacterial resistance to antibiotics is not an option. Considering that more than 20,000 European citizens die annually from untreatable bacterial infections, Europe and its member states should find the courage and creativity to financially, technically and legally support the introduction of phage therapies throughout Europe.

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CONFLICT OF INTEREST

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2. Roberts R *et al* (2009) Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. *Clin Infect Dis* **49:** 1175–1184
3. Barr JJ *et al* (2013) Bacteriophage adhering to mucus provide a non-host-derived immunity. *Proc Natl Acad Sci USA* **110:** 10771–10776

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